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Systematic Review and Meta-Analysis

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Published in:
Journal of Pediatric Gastroenterology and Nutrition

DOI:
[10.1097/MPG.0000000000002789](https://doi.org/10.1097/MPG.0000000000002789)

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2020

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Verkade, H. J., Thompson, R. J., Arnell, H., Fischler, B., Gillberg, P-G., Mattsson, J. P., Torfgård, K., & Lindström, E. (2020). Systematic Review and Meta-Analysis: Partial External Biliary Diversion in Progressive Familial Intrahepatic Cholestasis. *Journal of Pediatric Gastroenterology and Nutrition*, 71(2), 176-183. <https://doi.org/10.1097/MPG.0000000000002789>

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Systematic Review and Meta-analysis: Partial External Biliary Diversion in Progressive Familial Intrahepatic Cholestasis

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ABSTRACT

Objectives: We assessed available data on impact of partial external biliary diversion (PEBD) surgery on clinical outcomes in patients with progressive familial intrahepatic cholestasis (PFIC).

Methods: We performed a systematic literature review (PubMed) and meta-analysis to evaluate relationships between liver biochemistry parameters (serum bile acids, bilirubin, and alanine aminotransferase [ALT]) and early response (pruritus improvement) or long-term outcomes (need for liver transplant) in patients with PFIC who underwent PEBD.

Results: Searches identified 175 publications before September 2018; 16 met inclusion criteria. Receiver operating characteristic (ROC) analysis examined ability of liver biochemistry parameters to discriminate patients who demonstrated early and long-term response to PEBD from those who did not. Regarding pruritus improvement in 155 included patients in aggregate, 104 (67%) were responders, 14 (9%) had partial response, and 37 (24%) were nonresponders. In ROC analyses of individual patient data, post-PEBD serum concentration of bile acids, in particular, could discriminate responders from nonresponders for pruritus improvement (area under the curve, 0.99; $P < 0.0001$; $n = 42$); to a lesser extent, this was also true for bilirubin (0.87; $P = 0.003$; $n = 31$), whereas ALT could not discriminate responders from nonresponders for pruritus improvement (0.74; $P = 0.06$; $n = 28$). Reductions from pre-PEBD values in serum bile acid concentration (0.89; $P = 0.0003$; $n = 32$) and bilirubin (0.98; $P = 0.002$; $n = 18$) but not ALT (0.62; $P = 0.46$; $n = 18$) significantly discriminated decreased aggregate need for liver transplant.

Conclusion: Changes in bile acids seem particularly useful in discriminating early and long-term post-PEBD outcomes and may be potential biomarkers of response to interruption of enterohepatic circulation in patients with PFIC.

Key Words: bile acids, cholestasis, intrahepatic cholestasis, pediatrics

(*JPGN* 2020;71: 176–183)

Received October 10, 2019; accepted April 27, 2020.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.jpgn.org).

This study was sponsored by Albireo AB. Medical writing and editorial assistance were provided by Peloton Advantage, LLC, an OPEN Health company, and funded by Albireo Pharma, Inc.

H.J.V. is a consultant for Albireo AB, Ausnutria, GMP-Orphan, Intercept, Mirum, Vivet, FrieslandCampina Dairy Foods, and Danone/Nutricia

What Is Known

- In progressive familial intrahepatic cholestasis, disruptions in bile acid transportation lead to progressive and often life-threatening liver disease.
- Surgical interventions include interruption of enterohepatic circulation via partial external biliary diversion.

What Is New

- In this meta-analysis, we evaluated relationships between liver biochemistry parameters on the one hand and early response (pruritus improvement) and long-term outcomes (need for liver transplant) on the other hand in patients with progressive familial intrahepatic cholestasis who underwent partial external biliary diversion.
- Our findings suggest that bile acids and bilirubin levels may be useful as potential biomarkers in predicting both early response and long-term outcomes after partial external biliary diversion.

Progressive familial intrahepatic cholestasis (PFIC) is a family of ultra-rare inherited disorders characterized by disrupted bile homeostasis, debilitating pruritus, elevated serum bile acid levels, and potentially fatal liver disease (1–6). Pathologies underlying PFIC

Research. R.J.T. is a consultant for Albireo, Shire, Mirum Pharma, Generation Bio, Alnylam, Sana Biotechnology, and Qing Bile Therapeutics, and he has stock options in Generation Bio and Qing Bile Therapeutics. H.A. is a consultant for Albireo, Alexion, Baxter, Mirum, and Shire. B.F. has attended an advisory board meeting with Albireo. P.-G.G., and J.P.M. are employees of Albireo AB and may own stock/stock options in Albireo Pharma, Inc. K.T., and E.L. are former employees of Albireo AB, and may own stock/stock options in Albireo Pharma, Inc. Copyright © 2020 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

DOI: 10.1097/MPG.00000000000002789

include deficiencies in familial intrahepatic cholestasis 1 protein (FIC1), bile salt export pump (BSEP), and multidrug resistance 3 protein (MDR3) (7).

Currently, there are no approved medical treatments for patients with PFIC (1). Treatments used off-label for symptom relief or to counter the detrimental effects of cholestasis include fat-soluble vitamins, ursodeoxycholic acid (UDCA), cholestyramine, rifampicin, and antihistamines (8). Medical treatment, however, often fails, necessitating surgical intervention (1). Surgical approaches include strategies to interrupt the enterohepatic circulation, such as partial external biliary diversion (PEBD), partial internal biliary diversion, ileal exclusion/bypass, or gallbladder-colonic bypass, and, in the most severe/advanced cases and/or upon failure of other treatments to sufficiently relieve symptoms, liver transplantation (4,9,10). In PEBD, which is commonly used in FIC1-deficient and BSEP-deficient PFIC but is not a standard treatment for MDR3-deficient PFIC, a jejunal conduit from the gallbladder to the abdominal wall partially diverts bile to a permanent stoma (10). PEBD surgery, if performed before advanced liver disease has developed, reduces serum bile acids and pruritus and can improve long-term outcomes in patients with PFIC (9,11). Some patients, however, experience complications related to the external stoma (9,12), and approximately 25% of patients with PFIC fail to respond to PEBD (10). Understanding the relationships between laboratory parameters and clinical responses/outcomes to therapeutic interventions would be valuable to assess whether potential biomarkers for short- or long-term outcomes would be useful for evaluating new treatment approaches in patients with PFIC. Unfortunately, available data are limited to small studies, case reports, and case series.

Using data from published reports, this systematic literature review and meta-analysis assessed whether liver biochemistry parameters of serum bile acids, bilirubin, and alanine aminotransferase (ALT) could discriminate responders from nonresponders for early responses (effect on pruritus) and long-term outcomes (death or decreased aggregate need for liver transplant) in PFIC patients who underwent PEBD.

METHODS

Literature Search

The systematic literature search included studies reporting liver biochemistries and short- and long-term findings for patients with PFIC who underwent PEBD surgery. We searched PubMed for studies published before September 30, 2018 using the terms “biliary diversion” or “cholestasis.” Resulting publications were searched for the following: “external bile/biliary diversion” and “PFIC,” “progressive familial intrahepatic cholestasis,” or “Byler’s disease.” Other diagnoses (eg, Alagille syndrome, biliary atresia) and procedures (eg, internal bile diversion, ileal bypass, or ileal exclusion) were excluded. All studies reporting pre- and post-PEBD liver biochemistry values (serum bile acids, bilirubin, and ALT) and ≥ 1 short- or long-term clinical outcome were eligible for inclusion in the meta-analysis. Publications that reported results descriptively (eg, “lowering” or “normalization”), without numerical values, were excluded.

Meta-Analysis

The meta-analysis included all publications with extractable individual patient data. Consistently available liver biochemistry parameters are included in this report. It was assumed that the term bilirubin meant total serum bilirubin. In addition, authors of publications identified in the literature search were contacted to

determine if they were willing and able to contribute individual data if only grouped data had been published.

Receiver operating characteristic (ROC) analysis (SAS[®] version 9.4 [SAS Institute Inc., Cary, NC] using PROC LOGISTIC) was conducted to assess whether liver biochemistry parameters could discriminate PFIC patients who demonstrated early and long-term responses to PEBD from those who did not. ROC curves based on liver biochemistry parameters were explored using post-PEBD levels, absolute reductions, and relative reductions (expressed as percentages, compared with pre-PEBD levels). The ability of each parameter to distinguish PEBD responders and nonresponders was assessed based on statistical significance of the area under the ROC curve (AUC; null hypothesis: AUC = 0.5).

Responses to PEBD surgery were defined as “pruritus improvement” for early response and “decreased aggregate need for liver transplant” for long-term response. Despite no consistent definition for early response across all publications, pruritus improvement was considered an early response as all publications included pruritus improvement as at least part of the definition. When early response was based on multiple measures, “partial response” was defined as (at least) improvement in pruritus but not in all measures. To dichotomize results for the ROC analysis, partial responders were grouped with nonresponders. Long-term responders were defined as patients who did not receive liver transplant and/or did not die in the period of the respective report. Nonresponders were those who died or required liver transplant.

RESULTS

Literature Search

PubMed searches identified 175 publications (Fig. 1), of which, 16 met eligibility criteria and included pre- and post-PEBD liver biochemistry values and ≥ 1 clinical outcome in PFIC patients (9,12–26). Of these, 1 publication was excluded as patient’s liver biochemistry data could not be paired with clinical outcomes (26). An additional article (11) was identified through review of an article by the same authors (22) and was included as it provided additional long-term liver biochemistry data. This yielded a total of 16 publications eligible for meta-analysis across 155 PFIC patients (Fig. 1 and Table, Supplemental Digital Content 1, <http://links.lww.com/MPG/B841>). Median age at PEBD was 3 years (range: 5 months to 13 years). Reports included PFIC patients with deficiencies in FIC1, BSEP, or MDR3; in many cases, underlying genotypes conferring PFIC disease were not disclosed or evaluated. Although not included in the original publication, individual liver biochemistry data were provided by authors for 1 study (22) and were used in the current analysis (along with individual patient data from additional publications) in agreement with the authors and with ethical approval.

Liver Biochemistry Parameters Before Partial External Biliary Diversion

On the basis of aggregate and individual patient data, bile acids, bilirubin, and/or ALT were variable and substantially elevated before PEBD in patients with PFIC.

Bile Acid Levels Before Partial External Biliary Diversion

For pre-PEBD bile acid levels, results were available in 13/16 studies (142/155 patients). Across 6 studies (encompassing 100 patients with aggregate bile acid data), 3 reported pre-PEBD levels as means (range, 249–307 $\mu\text{mol/L}$) (13,14,17) and 3 reported

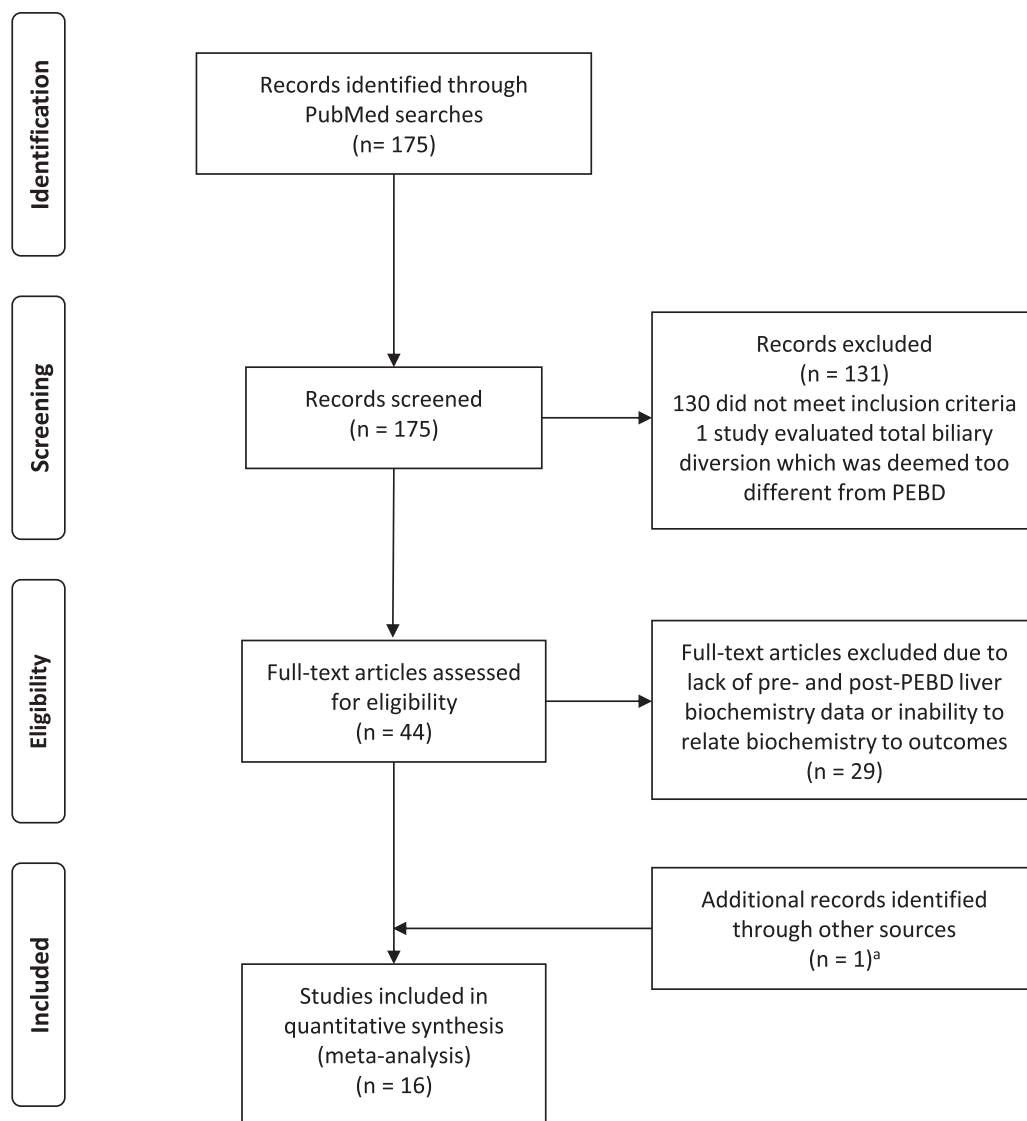


FIGURE 1. Diagram of screening and selection of included studies. ^aOne publication that contained long-term outcomes but lacked liver biochemistry data (11) was added because it was found to be a follow-up to an article already included in the literature search that included liver biochemistry data for the same patients (22).

medians (range, 299–346 $\mu\text{mol/L}$) (9,15,16) that were approximately 25 to 35 times the upper limit of normal (ULN) of 10 $\mu\text{mol/L}$. Individual bile acid patient data were available for 42 patients across 7 studies (18,19,21–25) and were also elevated before PEBD (median [quartile 1; quartile 3 (Q1; Q3)], 259 [195; 344] $\mu\text{mol/L}$; Figure, Supplemental Digital Content 2A, <http://links.lww.com/MPG/B841>).

Bilirubin Levels Before Partial External Biliary Diversion

For pre-PEBD bilirubin levels, results were available in 13/16 studies (118/155 patients). In 6 studies with aggregate bilirubin data (encompassing 87 patients), 4 reported pre-PEBD levels as means (range, 8–75 $\mu\text{mol/L}$) (12–14,17) and 2 reported medians (33 and 41 $\mu\text{mol/L}$) (9,16). Individual bilirubin patient data were available for 31 patients across 7 studies (18–24).

Before PEBD, bilirubin was elevated well above the ULN (median [Q1; Q3], 76 [41; 115] $\mu\text{mol/L}$; Figure, Supplemental Digital Content 2B, <http://links.lww.com/MPG/B841>). In general, pre-PEBD bilirubin levels were well above the ULN of 17 $\mu\text{mol/L}$.

Alanine Aminotransferase Levels Before Partial External Biliary Diversion

For pre-PEBD ALT levels, results were available in 9/16 studies (82/155 patients). Across 4 studies with aggregate ALT data (encompassing 54 patients), 2 reported ALT levels as means (38 and 96 U/L) (13,14) and 2 reported medians (60 and 75 U/L) (9,16). Individual patient data were available for 28 patients across 5 studies (1 patient was excluded because of lack of baseline data) (18–20,22,24). Before PEBD, ALT was elevated well above the ULN of ~ 35 U/L in patients >2 years of age ($n=28$; median

[Q1; Q3], 105 [54; 192] U/L; Figure, Supplemental Digital Content 2C, <http://links.lww.com/MPG/B841>).

Partial External Biliary Diversion Surgery Early Response

Post-PEBD follow-up times evaluating effects of PEBD on pruritus ranged from 6 months to 3 years, although some publications reported pruritus improvement within days or weeks (14,18,19,21). Overall, 104 patients (67%) had an early response of pruritus improvement following PEBD, 14 (9%) showed a partial response, and 37 (24%) patients were nonresponders.

Partial External Biliary Diversion Surgery Long-term Response

For long-term response (decreased aggregate need for liver transplant), 3 studies including 34 PFIC patients who underwent PEBD reported individual patient data on liver biochemistry parameters and long-term outcomes (11,24,25). Median (range) follow-up duration was 2.5 (0.2–10) years in the liver transplant group and 8 (0.5–13) years for those who did not receive liver transplant. In patients who underwent PEBD, 13 (38%) of 34 needed a liver transplant and/or died during follow-up (nonresponders), and 21 (62%) did not receive liver transplant (responders).

Relationship Between Liver Biochemistry Parameters and Early Response

Relationships between liver biochemistry parameters (serum bile acids, total serum bilirubin, and ALT) and early response of pruritus improvement were examined using available individual patient data.

Bile Acids/Early Response

Seven studies with individual patient bile acid data for 42 patients evaluated pruritus improvement post-PEBD (18,19,21–25). Bile acid levels decreased in patients classified as responders (median [Q1; Q3] percent change, $-98 [-99; -97]\%$; $n=25$), partial responders ($-42 [-72; -32]\%$; $n=5$), and nonresponders ($-21 [-32; 34]\%$; $n=12$); absolute post-PEBD bile acid levels were generally lower in responders than partial or nonresponders (Fig. 2A). In the ROC analysis, absolute post-PEBD bile acid levels could discriminate PFIC patients with an early response (ie, improved pruritus) from those with partial or no response (AUC 0.99; $P<0.0001$; Fig. 2B and Table 1). Absolute reduction (AUC 0.79; $P=0.0017$) and percentage reduction (AUC 0.98; $P<0.0001$) in bile acids following PEBD also could discriminate responders from partial and nonresponders (Table 1).

Bilirubin/Early Response

Seven studies with individual patient bilirubin data for 31 patients evaluated pruritus improvement post-PEBD (18–24). Bilirubin levels decreased in patients classified as responders (median [Q1; Q3] percent change, $-84 [-93; -60]\%$; $n=24$), in 1 partial responder (-30% ; $n=1$), and in nonresponders ($-19 [-35; 41]\%$; $n=6$); absolute post-PEBD bilirubin levels were generally lower in responders than in partial or nonresponders (Fig. 2C). In the ROC analysis, absolute post-PEBD bilirubin levels could discriminate PFIC patients who demonstrated an early response of pruritus

improvement from those with partial or no response (AUC 0.87; $P=0.003$; Fig. 2D and Table 1). Absolute reduction (AUC 0.77; $P=0.0335$) and percentage reduction (AUC 0.83; $P=0.007$) in bilirubin levels following PEBD also could discriminate responders from partial and nonresponders (Table 1).

Alanine Aminotransferase/Early Response

Five studies with individual patient ALT data for 28 patients evaluated pruritus improvement post-PEBD (18–20,22,24). ALT levels decreased in patients classified as responders (median [Q1; Q3] percent change, $-51 [-75; 29]\%$; $n=21$) and in nonresponders ($-28 [-46; -10]\%$; $n=6$), with a small increase in 1 patient classified as a partial responder ($+4\%$; $n=1$). Absolute post-PEBD ALT levels were generally lower in responders than in nonresponders (Fig. 2E), but they did not significantly discriminate responders from partial and nonresponders in the ROC analysis (AUC 0.74; $P=0.06$; Fig. 2F). Likewise, absolute ALT reduction (AUC 0.59; $P=0.47$) and percentage reduction (AUC 0.61; $P=0.38$) did not significantly discriminate responders from partial and nonresponders (Table 1).

Relationship Between Liver Biochemistry Parameters and Long-term Response

Relationships between serum bile acids, total serum bilirubin, and ALT and long-term response of need for liver transplant were examined using available individual patient data.

Bile Acids/Long-term Response

Among 32 patients with available bile acid and long-term response data from 3 studies (11,24,25), 20 did not require liver transplant (responders) and 12 required liver transplant or died despite PEBD (nonresponders) (Fig. 3A). Median (Q1; Q3) post-PEBD bile acid levels were 6 (4; 155) $\mu\text{mol/L}$ (normalized in 12 patients) in responders and 258 (163; 298) $\mu\text{mol/L}$ in nonresponders, representing median (Q1; Q3) percent changes of $-98 (-99; -51)\%$ and $-28 (-50; 17)\%$, respectively. This suggested that lower post-PEBD bile acid levels are found in responders than in nonresponders (Fig. 3A). In the ROC analysis, absolute post-PEBD bile acid levels could discriminate patients who demonstrated a long-term response to PEBD (ie, those who did not require liver transplant) from those who required liver transplant or died despite PEBD (AUC 0.89; $P=0.0003$; Fig. 3B) as did percentage reduction (AUC 0.83; $P=0.002$) but not absolute reduction (Table 1).

Bilirubin/Long-term Response

Among the 18 patients with available bilirubin and long-term response data from 2 studies (11,24), 13 did not require liver transplant (responders) and 5 required liver transplant despite PEBD (nonresponders) (Fig. 3C). Median (Q1; Q3) post-PEBD bilirubin levels were 9 (8; 13) $\mu\text{mol/L}$ in responders and 77 (77; 118) $\mu\text{mol/L}$ in nonresponders, representing median (Q1; Q3) percent changes of $-92 (-93; -80)\%$ and $-33 (-35; -4)\%$, respectively. This suggested that in responders, post-PEBD bilirubin levels are lower than in nonresponders (Fig. 3C). In the ROC analysis, absolute post-PEBD bilirubin levels could discriminate patients who did not require liver transplant from those who did despite PEBD (AUC 0.98; $P=0.002$; Fig. 3D) as did absolute reduction (AUC 0.83; $P=0.03$) and percentage reduction (AUC 0.88; $P=0.02$; Table 1).

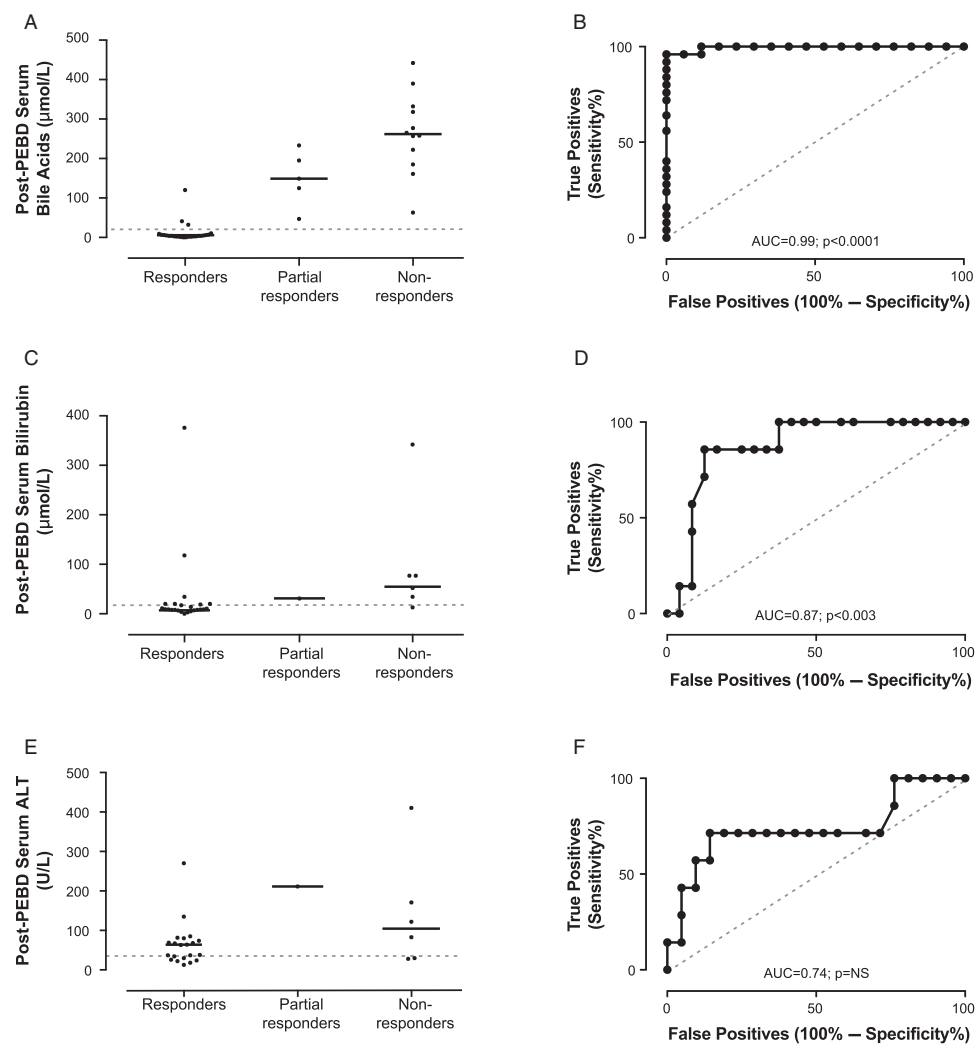


FIGURE 2. Post–partial external biliary diversion levels of liver biochemistry parameters and early response (pruritus improvement). (A) Post-PEBD bile acid levels in 42 patients grouped as responders, partial responders, and nonresponders from 7 studies (18,19,21–25). (B) ROC curve for post-PEBD serum bile acid levels and pruritus improvement. (C) Post-PEBD bilirubin levels in 31 patients grouped as responders, partial responders, and nonresponders from 7 studies (18–24). (D) ROC curve for post-PEBD serum bilirubin levels and pruritus improvement. (E) Post-PEBD ALT levels in 28 patients grouped as responders, partial responders, and nonresponders from 5 studies (18–20,22,24). (F) ROC curve for post-PEBD serum ALT levels and pruritus improvement. Solid horizontal bars indicate the median value for each group; dotted horizontal lines indicate upper limit of normal. ALT = alanine transaminase; AUC = area under the ROC curve; NS = not significant; PEBD = partial external biliary diversion; ROC = receiver operating characteristic.

TABLE 1. Ability of liver biochemistry parameters to discriminate responders from nonresponders: early and long-term responses			
ROC analysis	Bile acids AUC, <i>P</i> value	Bilirubin AUC, <i>P</i> value	ALT AUC, <i>P</i> value
Early response (pruritus improvement)			
Patients, n	42	31	28
Post-PEBD level	0.99, <0.0001	0.87, 0.003	0.74, 0.06
Absolute reduction*	0.79, 0.0017	0.77, 0.0335	0.59, 0.47
Percent reduction*	0.98, <0.0001	0.83, 0.007	0.61, 0.38
Long-term response (decreased need for liver transplant)			
Patients, n	32	18	18
Post-PEBD level	0.89, 0.0003	0.98, 0.002	0.62, 0.46
Absolute reduction*	0.65, 0.15	0.83, 0.03	0.68, 0.26
Percent reduction*	0.83, 0.002	0.88, 0.02	0.68, 0.26

ALT = alanine transaminase; AUC = area under the ROC curve; PEBD = partial external biliary diversion; ROC = receiver operating characteristic.
*Reductions from pre-PEBD levels.

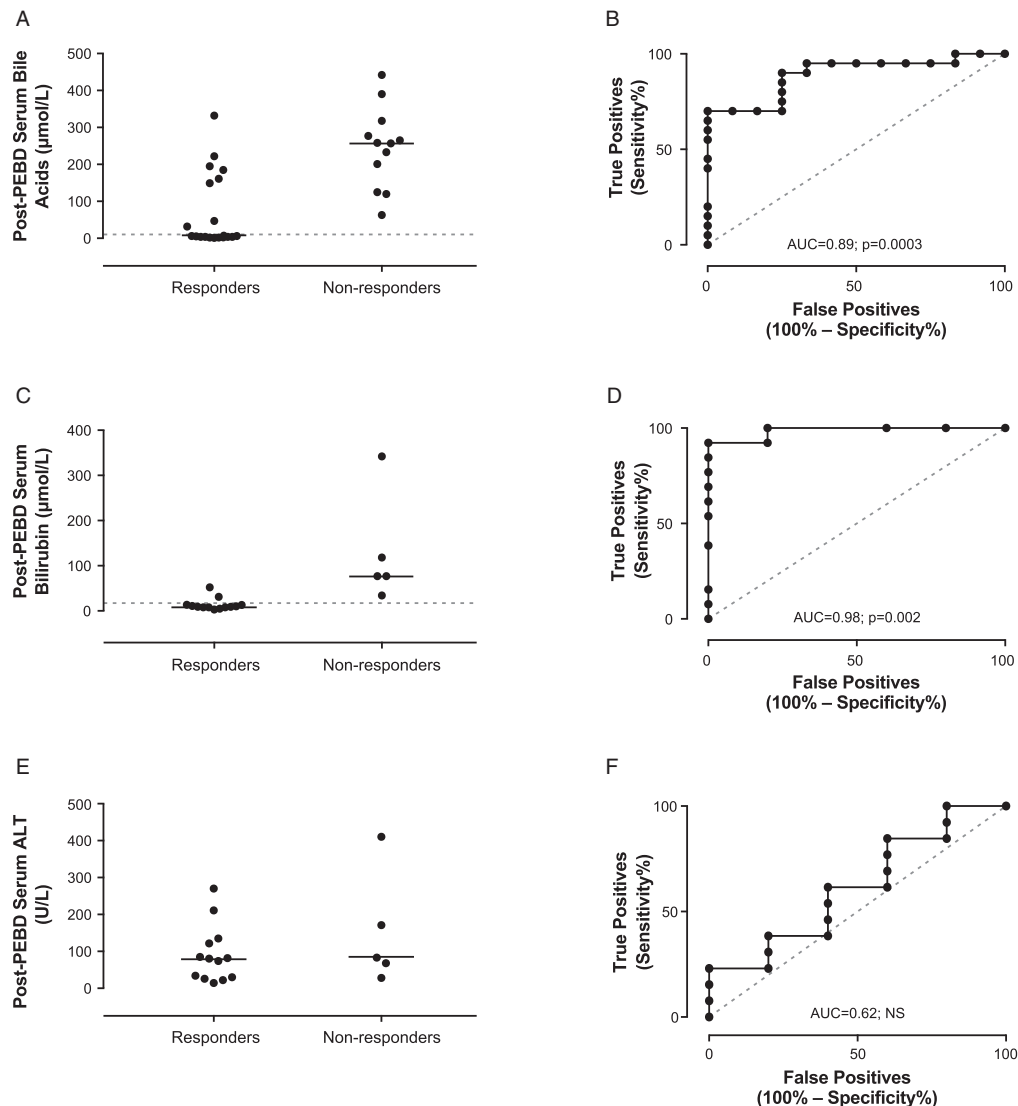


FIGURE 3. Post-partial external biliary diversion levels of liver biochemistry parameters and long-term response (decreased need for liver transplant). (A) Post-PEBD bile acid levels in 32 patients grouped as responders and nonresponders from 3 studies (22,24,25).^a (B) ROC curve for post-PEBD serum bile acid levels and decreased aggregate need for liver transplant. (C) Post-PEBD bilirubin levels in 18 patients grouped as responders and nonresponders from 2 studies (22,24).^a (D) ROC curve for post-PEBD serum bilirubin levels and decreased aggregate need for liver transplant. (E) Post-PEBD ALT levels in 18 patients grouped as responders and nonresponders from 2 studies (22,24).^a (F) ROC curve for post-PEBD serum ALT levels and decreased aggregate need for liver transplant. Solid horizontal bars indicate median value for each group; dotted horizontal lines indicate upper limit of normal. ^aBiochemistry data from Arnell et al (22); long-term response data from Arnell et al (11). ALT = alanine transaminase; AUC = area under the ROC curve; NS = not significant; PEBD = partial external biliary diversion; ROC = receiver operating characteristic; SD = standard deviation.

Alanine Aminotransferase/Long-term Response

Among 18 patients with available ALT and long-term response data (11,24), 13 did not undergo liver transplant (responders) and 5 underwent liver transplant despite PEBD (nonresponders) (Fig. 3E). Median (Q1; Q3) post-PEBD ALT levels were 80 (30; 122) U/L in responders (a reduction from pre-PEBD levels of 146 [58; 209] U/L) and 83 (68; 171) U/L in nonresponders (a reduction from pre-PEBD levels of 112 [52; 190] U/L), representing median (Q1; Q3) percent changes of -51 (-75; 4)% and -10 (-26; 15)%, respectively (Fig. 3E). In the ROC analysis of ALT levels, absolute post-PEBD (AUC 0.62; $P = 0.46$; Fig. 3F), absolute change (AUC

0.68; $P = 0.26$), and percentage change (AUC 0.68; $P = 0.26$) did not discriminate patients with a long-term response to PEBD from nonresponders (Table 1).

DISCUSSION

This systematic literature review and meta-analysis assessed available data on the impact of PEBD surgery on early and long-term outcomes in patients with PFIC. Our analyses indicate that PEBD reduces serum concentrations of bile acids and bilirubin, and that post-PEBD bile acid and bilirubin levels can discriminate responders from nonresponders for both early responses (effect on pruritus) and long-term outcomes (aggregate need for liver

transplant); post-PEBD ALT levels did not have this discriminatory ability. Our findings suggest that bile acid and bilirubin levels may be useful as potential biomarkers in predicting both early response and long-term outcomes after PEBD.

Our findings that PEBD impacts liver biochemistry parameters and pruritus are generally consistent with data from other recent studies, although there may be some overlap between patients in our study and those discussed below. A recent retrospective multicenter study found that 81% ($n = 17/21$) of FIC1-deficient patients and 76% ($n = 26/34$) of BSEP-deficient patients reported pruritus improvement (partial or complete) after undergoing PEBD (27). Serum bile acid and bilirubin levels also decreased significantly after PEBD. In a retrospective analysis from the Childhood Liver Disease Research Network (ChILDRen) that included 34 patients with PFIC (FIC1 deficiency, $n = 16$; BSEP deficiency, $n = 18$) (28), the proportion of patients reporting pruritus was significantly reduced following PEBD relative to presurgery values (65% vs 10% for FIC1-deficient patients; 50% vs 20% for BSEP-deficient patients; both $P < 0.0001$). There was also a trend toward reduced bile acid levels in these patients. Total serum bilirubin decreased significantly in FIC1-deficient patients but not in BSEP-deficient patients. No significant changes in ALT were observed. Two of 12 FIC1-deficient patients and 3 of 13 BSEP-deficient patients underwent liver transplant following PEBD. Unfortunately, neither study (27,28) analyzed relationships between bile acid or other serum parameter levels and clinical outcomes.

A recent retrospective follow-up study from the NAPPED (Natural Course and Prognosis of PFIC and Effect of Biliary Diversion) consortium found that native liver survival was significantly higher in BSEP-deficient patients who had undergone biliary diversion surgery than in those who had not (29), and a significant association was identified between lower postsurgical serum bile acids and long-term native liver survival (30).

Although the long-term benefits of PEBD are established in patients with PFIC, limitations such as need for a permanent stoma have spurred exploration of alternative surgical methods, including ileal exclusion and partial internal biliary diversion (8,16). At present, only a few reports are available that describe long-term results of these procedures, and the number of patients is low (8,31,32). The ileal bile acid transporter (IBAT) is a potential therapeutic target in patients with PFIC as it mediates resorption of 95% of intestinal bile acids (33,34), and IBAT inhibition represents a novel medical approach to interrupt the enterohepatic circulation. Our meta-analysis suggests that reductions in serum bile acids following interruption of enterohepatic circulation via PEBD can discriminate PFIC patients with pruritus improvement versus those without improvement, which could be useful for evaluating IBAT inhibitors like odeixibat (A4250) and maralixibat. In a phase 2 study of children with cholestatic liver disease that included 13 children with PFIC, reductions in serum bile acids significantly correlated with reductions in pruritus following odeixibat treatment (35). An interim analysis of a phase 2 study in children with PFIC showed an overall trend toward reduced bile acids and pruritus following maralixibat treatment (36).

Findings of our meta-analysis, together with studies describing interventions that interrupt enterohepatic circulation, such as PEBD or IBAT inhibition, provide insight into relationships between liver biochemistry parameters (eg, bile acids) and outcomes (eg, pruritus improvement, need for liver transplant, death) in children with intrahepatic cholestasis; future studies that better define these relationships are warranted.

This study has some limitations, including a retrospective design with limited access to raw and/or individual patient data. In addition, there were no uniform definitions for patient selection criteria or for early or long-term response based on validated rating

scales. Pruritus is difficult to quantify objectively as it involves physical sensations and emotional responses; therefore, this analysis utilized the responder categorization approach. Also, patients could not be analyzed by PFIC subgroup because of lack of information, including genotype data. Variability in surgical skill and experience as well as varying surgical approaches to PEBD and criteria/indications for choosing liver transplant may have contributed to differences in outcomes. There is a potential bias for publishing successful versus unsuccessful surgical reports. Finally, a relatively small number of patients was included in some analysis subgroups, and we cannot completely exclude the possibility that some patients included in this analysis were present in duplicate across utilized publications, as patient identities were not disclosed; this could reduce the number of unique patients in the current analysis. We also cannot exclude the possibility that additional studies fitting the search criteria may have been identified in other databases, such as EMBASE or the Cochrane Central Register of Controlled Trials. Additional research is needed to confirm results of this meta-analysis, including future studies investigating additional tools for evaluating the effects of therapeutic interventions for PFIC.

In conclusion, this meta-analysis of PEBD outcomes in patients with PFIC found that changes in bile acids and bilirubin were potential biomarkers for predicting early and long-term outcomes after PEBD. We speculate these parameters could also be utilized prospectively to evaluate other surgical or pharmaceutical approaches in these patients.

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